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Citation for final published version:

Ali, Faraz, Vyas, Jui and Finlay, Andrew Y. ORCID: <https://orcid.org/0000-0003-2143-1646> 2020. Counting the burden: atopic dermatitis and health-related quality of life. *Acta Dermato-Venereologica* 100 (12) , adv00161. 10.2340/00015555-3511 file

Publishers page: <http://dx.doi.org/10.2340/00015555-3511>
< <http://dx.doi.org/10.2340/00015555-3511> >

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Counting the Burden: Atopic Dermatitis and Health-related Quality of Life

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Atopic dermatitis is the most prevalent chronic inflammatory skin condition globally. The burden of atopic dermatitis on children and adults is extensive and there is also significant impact on the lives of patient caregivers and family members. It is important to be able to measure this impact to inform clinical decisions and to plan appropriate patient and carer support. The current impact of atopic dermatitis on children and adults can be measured using several different quality of life questionnaires: the most frequently used are the Dermatology Quality of Life (DLQI), Children's Dermatology Quality of Life and Infants Dermatology Quality of Life. The impact on partners and family can be measured using several atopic dermatitis specific questionnaires or the Family DLQI or the generic Family Reported Outcome Measure, FROM-16.

Key words: eczema; atopic dermatitis; quality of life; dermatitis.

Accepted May 7, 2020; Epub ahead of print May 15, 2020

Acta Derm Venereol 2020; 100; adv00161.

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The dry, itchy, eczematous skin of atopic dermatitis (AD) has a profound impact on quality of life (QoL). The pathophysiology of AD is postulated to be a combination of epithelial barrier defects, (1) immune system dysfunction (2) and psycho-neurogenic inflammation (3). The characteristics of AD are heterogeneous with varying clinical presentations according to age or anatomical region (4). AD has also been described as a systemic disorder given its wide-ranging associations from malignancies to cardiovascular effects (5). It is the most prevalent chronic inflammatory skin condition globally (6), but there are challenges in collating the extensive epidemiological data. Worldwide, up to 50% of cases labelled as AD are not in fact truly 'atopic' i.e. phenotypic eczema that is associated with circulating allergen-specific IgE. A phase two study of the largest AD sample in the world demonstrated a weak association between flexural eczema and atopy (7, 8) and therefore it cannot be assumed this presentation is always attributable to atopy. Furthermore *ad hoc* prevalence studies are often diverse and based on different diagnostic and sampling methods making true data comparison difficult.

SIGNIFICANCE

Atopic dermatitis is the most common inflammatory skin condition globally that affects both children and adults. The symptoms of atopic dermatitis as well as the demands of treatment often contribute to a significant impact on patient quality of life (QoL). This QoL impairment may also extend to caregivers, partners and close family members of atopic dermatitis sufferers. This review aims to evaluate the impact of atopic dermatitis on the QoL of patients and close relatives. A myriad of tools are available for measuring QoL; a brief description of the most relevant instruments is also presented in this article.

The burden of disease of AD on children is extensive and there is also significant impact on the lives of patient caregivers and family members (9). In affected adults, this effect is multi-dimensional with implications for mental health, work productivity and QoL. This review focusses on the measurement of QoL in AD patients, in particular on the QoL measures recommended by Harmonising Outcome Measures for Eczema (HOME), and the implications of the wider impact that AD has across different ages, social groups and countries.

Health-related quality of life (HRQoL) is a specific aspect of the wider concept of "quality of life". Throughout this manuscript "quality of life" refers to HRQoL.

EPIDEMIOLOGY OF ATOPIC DERMATITIS

The determination of accurate prevalence data for any disease depends on there being clear agreed diagnostic criteria and the ability to gather data from subjects that represent the general population. However, there are several differing diagnostic criteria that may be used in surveys of AD prevalence, contributing to confusion, and the methodology of many surveys leads to selection bias, for example if data from a clinic is measured rather than from a population cross-section. The various prevalence figures quoted in this review relate to the population described in the corresponding reference and may not be generalised to other populations.

Most AD epidemiological data have focussed on the paediatric population (9). The advent of the International Study of Asthma and Allergies in Children (ISAAC) has provided a standardised platform to identify over a

million children suffering with AD worldwide (10). The prevalence ranged from 0.9% (India) to 22.5% (Ecuador) in a sample of 380,000 children aged 6–7 years from 60 countries (11). For teenagers (ages 13–14, 660,000 subjects) the prevalence values range from 0.2% (China) to 24.6% (Columbia) with generally higher values seen in Latin America and Africa. In the European Union the point prevalence is 4.4% (12).

There have been several studies examining the adult population. The European Community Respiratory Health Survey (ECRHS) study collated data from US and European subjects and identified prevalence rates ranging from 0.3% (Switzerland) to 6.2% (Estonia) (13). Recently, Barbarot et al. (12) conducted an international survey on representative samples of adults (ages 18–64) worldwide using standardised methods and diagnostic criteria. Prevalence values ranged from 2.1% (Japan) to 8.1% (Italy), and there were further variations within countries and regions. Generally, there was a higher prevalence in females, but in the UK and the USA there was no significant difference in prevalence between females and males. Peak prevalence was from age 25 to 45 years, with AD then becoming less prevalent with increasing age ($p < 0.05$). However, a study limitation was that subjects self-diagnosed using modified UK Working Party criteria, with under 10% having a physician diagnosis. Regardless of which measure was used, USA subjects reported having the most severe AD, whereas in southern Europe the prevalence of mild disease was higher than in northern countries such as in the UK (12).

A systematic review of 13 studies conducted in the Netherlands and the UK demonstrated that the prevalence of AD assessed by general practitioners (1.8–9.5%) was lower than when self-reported (11.4–24.2%) (14). This may be because milder cases do not present to general practitioners, or self-reporting may over-diagnose. Kim et al. (15) analysed 110,000 cases and reported that the mean age of AD diagnosis was 1.6 years, with $< 5\%$ cases experiencing persistent disease at 20 years follow-up. Disease severity, duration, later onset and female sex were all associated with persistent disease.

As the above studies demonstrate, there is a large burden of disease from AD. It is imperative to measure the impact of this condition in those who are affected by it, because this information is essential to inform the clinician concerning choice of therapy. This data is also useful in the assessment of novel therapies, and in monitoring response to therapy.

PATIENT REPORTED OUTCOME MEASURES

A Patient Reported Outcome (PRO) is any report that comes directly from a patient about a health condition or its treatment, without interpretation by a clinician or anyone else (16). The initial drive for PROs was led by the pharmaceutical industry. In the US during the late 1980s there

was an increased awareness of the importance of patient input in assessing treatment. The seminal Rand Health Insurance experiment collected patients' self-report of health status to understand the impact of health insurance plans on health outcomes (17). Following this, Tarlov et al. (18) conducted an observational study to ascertain how outcomes of care were affected by specific components of the health care system. This landmark Medical Outcomes Study concluded that tools should be developed for "monitoring the patient wellbeing in office practice and clinical research." The Food and Drug Administration (FDA) initiated the requirement for QoL assessments in oncology trials (19). However, a report of a PRO measure used as an endpoint in a clinical trial involved anti-hypertensives: when the results were published by the press, although the endpoint measured tolerability rather than efficacy, the stock market value of the pharmaceutical company rose resulting in an economic impact of a health related outcome (20). The term "patient reported outcome" was coined in the year 2000 and the plethora of outcome measures subsequently developed led to the development of a PRO harmonisation group (21).

PROs may include evaluation of symptoms, functional status, or general or HRQoL.

THE IMPACT OF ATOPIC DERMATITIS ON QUALITY OF LIFE

QoL measurement has become an integral aspect of monitoring disease and intervention efficacy across dermatology. Three dimensions in particular have been proposed that are key to QoL evaluation: 'now', 'long-term' and 'family' (22). The 'now' is important for current assessment, but the long-term effects as well as wider implications for family should also influence treatment and health-economic decisions. It is vital to understand the various aspects of QoL impairment across the range of AD sufferers.

The impact of AD on children is comparable to other childhood chronic diseases such as cerebral palsy, epilepsy and cystic fibrosis (23). A review by Olsen et al. (24) identified data from 37 studies on 4082 children with AD and found that AD had, on average, a moderate effect on health-related QoL. However in each study there was a wide range of reported impacts of AD. Children with AD are often affected on a daily basis including problems when feeding, changing clothes and playing, thus depriving them of a 'normal childhood' (25). The chronicity of AD is often not a focus in studies: QoL scores may differ between primary and secondary care settings as the latter are likely to include more severe cases.

There are similar concerns for teens and adolescents. Parents fear that their children may be unable to make friends when older (26). Growing up, they develop a sense of being different due to alienating comments and having to explain several misconceptions (27), eventually

leading to a feeling of isolation and the need to be 'different' (28). Despite the debilitating nature of AD and the wider effect on school-work, AD does not impact academic performance in adolescents (29) and compliance with topical treatment in this group was reported in one study to be as high as 96% (30). Nevertheless, AD may influence career pathways. Advice to adolescents about work where having AD may involve risk is important to help them decide appropriate careers (31). The transition from paediatric to adult clinics is often a challenging period and the Department of Health in England has identified a specialised need in this area (32). A trial of 'young adult' clinics for AD patients with open access psychological support demonstrated significant improvement in QoL with high satisfaction rates.

AD has long been considered mainly a childhood problem, but the prevalence in adults ranges between 3–5% (33). In a review of two cohorts, 38% of adults with AD had symptom onset in childhood. (34). Over half of adult patients report that AD has a moderate to extremely large effect on their QoL. Many describe pain, stinging and embarrassment from their AD impacting their choice of clothing. The burden increases with increasing severity of disease (35): 57% of adults miss at least one day of work in the preceding year and describe problems with intimacy and feelings of guilt due to AD. Over 10% of 1189 people with moderate to severe AD demonstrated depressive symptoms (35). Of those subjects suffering from severe AD, 88% felt their ability to tackle life was at least partly compromised (35).

Whether the patient is a child, teenager or adult, AD impacts on the extended family as well as on caregivers, a concept described as 'The Greater Patient' (36). This effect may be experienced by anyone with a close relationship with the patient (37). This broader impact of disease is increasingly being recognised as another dimension of healthcare, with the advent of several new questionnaires to ascertain this impact. AD, being a common childhood condition, is a particularly relevant field of research given the 'web of relationships' involved from an early stage (38).

Several major life changing decisions, such as choice of education, choice of career, choice of partner or decisions about whether to have children may be influenced by having a chronic skin disease such as AD (39). The impact of the disease on such decisions can therefore alter the life course of people affected, with the impact of the disease echoing through the decades.

A BRIEF HISTORY OF QOL IN ATOPIC DERMATITIS

A plethora of QoL measures have been developed within dermatology, especially in psoriasis and AD. A systematic review by Rehal & Armstrong (40) in 2011 attempted to identify trends in outcome instruments used in AD trials.

Of the 382 studies included, only 67 studies incorporated QoL measurements. Eleven instruments were identified for measuring QoL, of which the Children's Dermatology Quality of Life (CDLQI) was the most frequently used followed by Dermatitis Family Index (DFI), Dermatology Life Quality Index (DLQI) and Infant Dermatology Quality of Life questionnaire (IDQoL). Three tools measured the QoL of family members of patients with AD: DFI, Parents Index of Quality of Life in Atopic Dermatitis (PIQoL-AD) and Parents of Children with Atopic Dermatitis (PQoL-AD). The authors surmised that an overall increase in use of QoL instruments from 1985 to 2010 indicated the emerging importance of QoL measures for patient evaluation and management.

HARMONISING OUTCOME MEASURES FOR ATOPIC DERMATITIS

Noting the myriad of outcome assessments for AD, the first International Conference on HOME was held in 2010 (41) and a decision was made for a core outcome set (COS) to be developed for AD. All scales had to pass the OMERACT filter of truth, discrimination and feasibility (42). The studies assessing the validity of different instruments were required to pass the COSMIN checklist (43). In 2011, 4 outcome domains were agreed on: symptoms, clinical signs, long-term control of flares and QoL (44). At the HOME III meeting Eczema Area and Severity Index (EASI) was recommended as the instrument for the outcome disease severity (45), HOME IV recommended Patient Oriented Eczema Measure (POEM) as the PRO for measuring symptoms (46). Heinal et al. (47) in 2016 conducted a study on QoL instruments used in eczema trials using the Global Resource of Eczema Trials (GREAT) database. In the 303 studies included from 2002–2014, approximately 90% of studies used a PRO, however only 63 used QoL measures. Eighteen named and 4 unnamed QOL instruments were found. Unlike the study by Rehal et al. mentioned above, (40), Heinal et al. (47) did not find evidence of increasing use of QOL measures, however confirming Rehal et al's finding, the DLQI, CDLQI, IDQoL and DFI were the most frequently used instruments. Four instruments measured the impact of AD on carers of patients of which two were named (DFI, PIQoL-AD).

Around the same time Hill et al. (48) conducted a systematic review looking at trends in disease severity and QoL instruments for patients with AD. Only 45 of the 135 identified studies measured QoL. Again, the DLQI, CDLQI, IDQoL and DFI were the most commonly used instruments. Hill et al. found 28 QoL measures in contrast to the 22 reported by Heinal and colleagues (47), possibly due to the different databases searched. Hill et al. (48) also found that the number of articles reporting on QoL peaked in 2012. Three instruments (DFI, FDLQI and PIQoL-AD) measured impact of QoL on caregivers.

HOME V concentrated on the definition core outcome for long-term control and its measurement as well as future areas of research for a tool to measure children's QoL (49). It was agreed that a new instrument should be developed for long-term control and that further research on itch intensity was necessary. It was also decided that none of the QoL instruments could be recommended at that point in time due to concerns with validation in certain areas.

However, the sheer number of QoL instruments in the above studies, with some instruments used only in single studies, highlighted the importance of standardised methods for measuring QoL in AD in order to compare various intervention measures. Therefore, at the 2019 HOME VII meeting (50) it was agreed to recommend DLQI and CDLQI to measure the QoL of adults and children and the proxy measure IDQoL to measure the QoL of infants. Two new instruments which had been developed in response to the recommendations from HOME V, Atopic Dermatitis Control Test (ADAPT) and Recap of Atopic Eczema (RECAP) were recommended for measuring long-term control. In addition, the Numerical Rating Scale (NRS-11) (51) to measure the intensity of itch was recommended in addition to POEM as the PRO to measure symptoms. It was also agreed that the COS for AD should be measured at baseline and end of the primary endpoint to ensure comparability in trial results.

QUALITY OF LIFE INSTRUMENTS FOR ATOPIC DERMATITIS CHOSEN BY THE HOME INITIATIVE

Historically, the value of clinical research has been reduced by different outcome measures being used in individual studies, making comparison impossible. The HOME initiative, by identifying a set of core measures provides the potential for improved assessment, comparison and combination of data.

Dermatology Life Quality Index

The DLQI is a dermatology-specific questionnaire developed in 1994 (52). There are over 110 translations, used in over 80 countries (53). The DLQI is quick and easy to perform and score in routine clinical practice. During the initial development, 120 patients answered the open-ended question "list all the ways your skin disease affects you". The questionnaire was developed from the answers.

The DLQI is a 10-item questionnaire with a one week recall period. It is completed, on average, in two minutes. The DLQI assesses the impact of skin disease on symptoms and feelings, daily activities, leisure, work and school, personal relationships and the impact of treatment. The ten question scores (each 0–3) are added to give the DLQI score (maximum 30).

The DLQI has been extensively validated in numerous studies with regards to its psychometric properties as well as its use in clinical research (54–56). The DLQI structure has been examined with respects to dimensionality

indicating one to 4 factors across various studies (54). It is responsive to change (57, 58) with high test–retest reliability (59, 60).

The DLQI validated score banding (61) allows meaningful score interpretation. For example, score band 0–1 indicates no effect on a patient's life and 11–20 a large effect. This banding can help inform clinical decisions. The DLQI has been significantly correlated with numerous other measures highlighting its construct validity (54), and used as the standard comparator in the validation of many novel QoL questionnaires. The DLQI has been mapped to the EQ-5D using ordinal logistic regression allowing the prediction of dermatology-specific utility values from generic EQ-5D scores (62). The model allows the capture of disease-specific data that generic measures are often unable to capture, thereby generating more precise health economic data without the need for utilising multiple questionnaires. However, though the model is validated for large groups of data, it requires further testing at an individual subject level. An electronic format has been developed and validated against the paper format demonstrating equivalence (63).

Although the DLQI is the most commonly used measure across dermatology (55, 64), several limitations have been described including concerns regarding under-representation of emotional aspects and its uni-dimensionality (65). Furthermore, there are concerns over score interpretation when "not relevant" options are chosen. In the DLQI, for 8 of the 10 items it is possible for the respondent to choose "Not relevant". If the subject does this for one question, because the life aspect enquired about is not part of the respondent's usual life pattern, then the overall maximum score is reduced. The more questions that are answered "not relevant" the greater the impact on the maximum possible score. Some subjects might therefore not reach a critical level that is used to help inform a clinician concerning the use of some therapy, even though the reason that a question may be "not relevant" may be that the skin disease has severely impacted that aspect of the respondent's life. It has therefore been suggested that the final score should be adjusted depending on the number of "Not relevant" answers given (66).

However, introducing an additional more complicated scoring system may not be appropriate (67) and would be impractical in busy clinics, require a wide range of revalidation studies to be performed and introduce confusion into the interpretation of DLQI scores (68). Whatever method is used to calculate them, DLQI scores should be used to help the clinician take the most appropriate decision for individual patients, and not used to restrict clinical judgement. A simple approach would be for any clinician reviewing a completed DLQI, or indeed any QoL questionnaire, to note whether or not there were any "Not relevant" answers, to enquire further and to take this into account as part of the information informing their clinical decisions.

Although many properties of the DLQI have been extensively validated, the DLQI has been criticised for not having been subject to Rasch analysis (69, 70), a method for the refinement of items and to convert the ordinal scale to a fundamental measure. However, the high face validity of the questions, the simplicity of its use and the easy interpretability of its scores have led to the DLQI being the first QoL measure with which dermatologists worldwide have become familiar (71), contributing to a cultural shift towards patient-centred medicine. Many clinicians have embedded the use of the DLQI in their routine practice because of their experience of its usefulness in routine clinical care, and the DLQI is incorporated in national guidelines or registries in at least 40 countries.

The DLQI has been recommended by the HOME initiative as the core instrument for measuring the impact of AD on the QoL of adult patients with AD (50).

Minimal Clinically Important Difference

The minimal clinically important difference (MCID) is the minimal change in score considered clinically significant by clinicians and patients (72). This provides additional meaning to QoL score changes. The DLQI MCID value is 4 points (73). We have proposed a 'multiple-MCID' concept has (74) to allow a more distinguishing analysis of interventional studies. However, this requires extensive further validation.

Children's Dermatology Life Quality Index

The CDLQI measures the impact of skin conditions on the QoL of children aged 4–16 years (75). A 10-item questionnaire was developed, based on 169 replies from children, asking how their skin condition affected their life. The CDLQI measures impact over the last week on symptoms and feelings, leisure, school or holidays, personal relationships, sleep and treatment. One question has a choice of two options dependent on whether or not within the last week the child was in school or on holiday. Each question has 4 possible answers. A cartoon version appeals to younger children (76). The CDLQI has been validated extensively (77–79). It is completed in mean in 2 min and has score bands to give meaning to the scores (80). There is no published minimal clinically important difference (MCID) for CDLQI described for use across all skin diseases. However, for use in children with AD it has been suggested that the MCID for the CDLQI is between 6–8 points (81).

The CDLQI has been recommended by HOME as the core QoL instrument for measuring the impact of AD on the QoL of children (50).

Infants' Dermatitis Quality of Life index

The IDQoL is a dermatitis specific parent/caregiver proxy measure of the QoL of children under the age of 4 years (82). It is a 10-item questionnaire with a one week recall

period. The items measure the perceived impact on QoL of itch and scratch, mood, time to sleep, playing or swimming, family activities, mealtimes, treatment, dressing and undressing, and bath time. An additional question records the severity of dermatitis as perceived by the parent/caregiver. The IDQoL had been translated into several languages and is frequently used in AD trials and validation aspects have been described (83). The IDQoL has been recommended by HOME as the core QoL instrument for measuring the impact of AD on the QoL of infants (50).

The core measures chosen may change in the future if more appropriate measures are developed, but there is huge strength to be gained by always using the same set. The minimal clinically important difference and descriptive score meaning bands have not been described for the IDQoL.

Disability adjusted life years

Whereas Quality Adjusted Life Years (QALYs) are years of healthy life lived, Disability Adjusted Life Years (DALYs) are years of healthy life lost. To calculate the burden of a certain disease, the disability weighting is multiplied by the number of years lived in that health state and is added to the number of years lost due to that disease (84). Using DALYs, the global burden of skin disease survey revealed that eczema causes the highest burden of all skin diseases worldwide (85). Eczema is one of top 50 most common causes of disease, with a global prevalence estimated at 229 million people affected. However, it must be remembered that AD affects the QoL of not only those directly affected but also their close family members.

FAMILY IMPACT OF ATOPIC DERMATITIS

Impact on parents

AD is a chronic disease so the symptoms require constant attention. Treatment for AD includes regular use of emollients along with various topical and systemic measures. The treatment process can have an adverse impact on the QoL of the patient (86) and also the main caregivers, especially when young children are affected. Inevitably parents are affected too. A meta-ethnography study (87) collated parental and childhood/adolescent experiences of AD. It is postulated that parent and child bonding is affected as skin irritation may limit physical interactions (88). Furthermore, the associated behavioural difficulties such as restlessness and hyperactivity may be demanding for parents, resulting in frustration and exhaustion (89). Parents may choose not to have further children because of the current burden on the wider family. Dedication time for treatment application and extra housework also directly impacts parental work responsibilities and therefore has financial implications (90). The symptoms experienced by children e.g. sleep disturbance, restlessness, psychological strain and embarrassment may all be experienced

second hand by parents and therefore their QoL is a key determinant of the child's well-being (26, 91).

Parents report having to apply creams that children dislike, often resulting in the need for coercion (92). Cultural issues may play an important role in parental attitudes to their affected child. Mothers may feel they did something wrong during pregnancy, or develop a sense of guilt for neglecting other children because of their focus on the child with AD (91). Anxiety may be exacerbated by conflicting advice on management, including the long-term sequelae of topical corticosteroids being inadequately explained by health professionals (93).

Loss of sleep is another familiar theme in parents of children with AD. Angelhoff et al. (94) conducted a study into the perceptions of sleep in such parents. Eleven mothers and one father, with children aged 0–2 years with SCORing Atopic Dermatitis (SCORADs) of >15 were interviewed. All but one parent experienced fragmented sleep. Most parents accepted the sleep loss but expressed a desire for longer uninterrupted sleep. Sleep loss led to fatigue with parents perceiving this had a negative effect on the whole family. The participants felt that the sleep loss was normalised by other family members and ignored by health professionals. The participants also felt that dynamics between parents and other siblings had changed, leading to feelings of guilt and sadness.

Moore et al. (95) reported that parents of children with eczema suffered sleep loss, with the mothers losing a median of 39 min and fathers a median of 45 min of sleep. In contrast, parents of children with asthma lost no sleep. While both parents of children with AD had increased anxiety scores, the mothers had two-fold higher scores of depression than mothers of children with asthma. This was related more to the sleep loss than to a direct effect of the eczema.

In contrast, in an ongoing large prospective, longitudinal, population-based cohort study 11,649 mother–child pairs in the UK were followed up by Ramirez et al. (96) from birth to 10 years. Children were classified as having AD on the basis of the presence of flexural dermatitis on two occasions. After adjusting for confounders, sleep duration and early morning awakening were similar in mothers of children with active AD and mothers with children never having reported AD. However, difficulty in falling asleep, subjectively insufficient sleep and day-time exhaustion were more frequently reported in mothers of children with active AD. The authors also reported larger effects in mothers of children with more severe AD. Adjusting for child sleep disturbances did not change the conclusions, and other factors such as anxiety and stress related to caring for children with AD may have been contributory.

Pustisek et al. (97) studied the QoL of 171 parents (mean age 32 years) of children with AD in Croatia. The mean FDLQI score (range 0–30) was 13.6 ± 6.0 , indicating a major effect on the QoL of parents. The most frequently

recorded problems were time spent looking after the child, household expenditure and emotional distress, as in a Ukraine study (98). The mean Perceived Stress Scale score was 20.0 ± 5.8 , 7 points higher than the average person aged 30–40 years, indicating higher stress levels in parents of children with AD and a correlation with QoL.

The impact of a child's eczema on the QoL of mothers and fathers may vary. Marciniak et al. (99) assessing parents QoL with the FDLQI, found that children's AD had a greater impact on the QoL of mothers than of fathers. Whilst the impact on the social life, spare time and daily expenditure was similar, mothers' relationships with other people were more affected than fathers' relationships with others, however the greatest impact on fathers was on their work or education. This was in contrast to the study by Pustisek et al. (97) where work or education were the lowest scoring items on the FDLQI: this could be because most participants in Pustisek's study were female with over half on maternity leave or unemployed.

Counter-intuitively, there may be positive outcomes resulting from a child suffering with AD. Parents may develop a strengthened bond with their children through the extra time spent treating and supervising them (100). To stop children from scratching, parents spend more time holding children closer, and balanced with the discomfort of physical symptoms, this overall creates a deeper emotional closeness (26). Parents also feel empowered by learning about AD and educating others about this debilitating condition (87).

Impact on siblings

Basra & Finlay proposed the term "Greater Patient" to encompass the interdependence of patients with their close relations (36). In childhood AD this includes the parents, who are generally the caregivers, however, in childhood siblings usually live together and their lives may also be affected. Whilst there are many studies on the QoL of siblings of children affected with other medical conditions, notably cancers (101–106), there is a lack of information on the impact of QoL on siblings of children affected with skin conditions, including AD. It is difficult to compare from the literature the effect on the QoL of siblings of skin disease compared to other diseases, due to the wide variety of instruments that have been used. Siblings of children with chronic conditions may have the same QoL as their peers (107), but it has also been suggested that siblings may have increased levels of distress (102). The parent child relationship and the sibling bond may also be affected when a child in the family has a chronic condition (108).

These negative interactions with family members (94, 99) coupled with sleep deprivation can leave patients, and their carers, feeling exhausted, stressed and depressed (96, 97). There may therefore be repercussions on siblings of patients affected with AD: this area needs further investigation.

The above findings illustrate the importance of assessing the QoL of family members. Several dermatology specific and AD specific validated instruments exist for measuring the impact of QoL on family members of patients with AD. The HOME initiative has not yet addressed this. However, the TREATment of ATopic eczema (TREAT) Registry Taskforce has recommended that for research registries for paediatric and adult patients with AD, if family impact is measured, the Family Dermatology Life Quality Index (FDLQI) should be used (109).

QUALITY OF LIFE INSTRUMENTS FOR FAMILY MEMBERS

Family Dermatology Life Quality Index

The FDLQI is a 10-item questionnaire, with a recall period of one month, assessing the impact on the QoL of adult family members of people of any age with any skin condition (110). The questionnaire includes the domains of emotional and physical wellbeing, relationships, leisure activities, social life, burden of care, impact on job/study, housework and expenditure. Each question is scored on a 4-point scale (0–3). The FDLQI has been translated into several languages (111) and has been used in various studies involving AD and other dermatological conditions (97, 99, 112–116).

Dermatitis Family Index

The DFI, the first family QoL questionnaire in dermatology measures the impact of having a child with AD on the QoL on their adult family members (117). This 10-item dermatitis specific questionnaire measures the impact over the last week on QoL in the domains of housework, food preparation and feeding, sleep of others in the family, family leisure activities, time spent on shopping, expenditure, tiredness, emotional distress, relationships and impact of child's treatment. Each question is scored from 0–3 points. There are no validated banding descriptors for the DFI, but some studies have used non-validated scoring descriptors (118, 119). The DFI has the advantage of being eczema specific and its measurement properties have been reviewed (120). The DFI, along with DLQI, CDLQI and IDQoL is one of the most frequently used instruments for measuring QoL in eczema studies (40, 47, 121).

Parents Index of QoL in Atopic Dermatitis

The PIQoL-AD is another AD specific measure to assess the impact of the child's AD on the QoL of parents (122). Developed on the basis of multinational qualitative interviews with parents of children up to age 8 years with AD, this is a 28-item unidimensional questionnaire (123). The lower the score, the better the QoL, a change of 2–3 PIQoL-AD points over time is considered meaningful.

Childhood Atopic Dermatitis Impact Scale (CADIS)

CADIS is a QoL measure for parents of children with AD combined with a proxy measure for children under the age of 6 years (124). It measures the impact on QoL of the domains of symptoms, activity limitations and behaviour, family and social function, parent sleep and parent emotion. This 45-item questionnaire uses 5-point Likert Scales giving a maximum score of 180. The recall period is the last 4 weeks and the questionnaire can be completed in approximately 6 min (125). Whilst it does not have score band descriptors, the MCID is considered to be a 12% change from the total score or a 12% change from any of the individual domains (126).

Family Reported Outcome Measure

Speciality and condition specific questionnaires cannot compare the impact on QoL of family members between different specialities. Golics et al. (127) developed the Family Reported Outcome Measure (FROM-16), based on relatives of patients from 26 medical specialties.

FROM-16 has 16 questions and can be used to assess the QoL of any adult member of the family of a patient of any age with any disease. The average completion time is 2 min. FROM-16 consists of the Emotional domain with 6 questions and the Personal and Social Life domain with 10 questions. Each question has three possible answers: 'Not at all', 'A little' and 'A lot' scoring 0, 1 and 2, respectively. Validation studies have been completed in Germany and Thailand and further validation characteristics are being studied. FROM-16 can be used to compare the QoL of family members across different disciplines in medicine, thus making it easier to make meaningful comparisons in QoL trials involving different medical conditions.

The Impact on Family Scale (IOF) (128, 129) has been validated to measure the impact of QoL on the adult family members of children suffering with chronic illness or disability. However, unlike the FROM-16, which can be used in the family members of patients of any age, the IOF should only be used for family members of affected children.

DISCUSSION

In any scientific endeavour, it is essential to be able to measure some characteristic of what is being studied. Without measurement, it may be possible to describe, but impossible to make meaningful comparisons or detect change. It could almost be said that if you can't measure something, it doesn't really exist, at least to a scientist. The same applies in medicine, a field of science that co-exists as an 'art'. Advances have followed the ability to measure: measuring blood pressure has enabled identification and control of hypertension, measuring visual fields has allowed diagnosis of ophthalmic and neurolo-

gical conditions and measuring frequency of micturition is used as an alert to diabetes and prostatic hypertrophy. Perhaps because of the visual nature of dermatology, a focus on measurement came late to our subject. But this delayed focus has coincided with a realisation that, as part of delivering the highest quality of care, we need to better understand what our patients are experiencing (130). In addition, qualitative studies should be used more often in combination with quantitative studies to gain more insight into the real burden of diseases such as AD.

This review has focussed on questionnaires specifically designed to measure the impact on QoL of skin diseases in general or of AD in particular. However, there are also a wide range of questionnaires that are designed to be used across all diseases. Examples of such measures include the Short-Form 36, the WHOQOL and EuroQoL (EQ-5D). Utility information giving QALY information is typically calculated from EQ-5D data, and this is sometimes used by national or international drug regulation agencies to inform decisions concerning resource allocation. However, use of QoL data in this way may overlook critical aspects of the reality of the impacts of skin diseases, such as the psychological impact that understanding the risk of mortality, say of a malignant melanoma, may have. And having a basal cell carcinoma that is treated appropriately may have a low impact on QoL, but if untreated the long-term consequences can be extremely serious. Therefore, when QoL measures are used to inform resource allocation, wider aspects of the conditions must also be considered.

This review has described some of the many ways in which the lives of people with AD are affected by their condition. Large multicentre studies in Europe and the USA determined that patients with psoriasis felt that their dermatologists were not aggressive enough with therapy: it is likely that the same applies at least to adult AD. By having insight into the individual patient's experience, more appropriate therapeutic decisions may be made, especially over the coming decade with the advent of many novel powerful systemic therapies for AD.

The Greater Patient, the close family members, may all experience impact on their QoL through having a family member with AD. But the "Greater Patient" also acts as the "Greater Therapist", as family members support the patient with practical therapeutic help, such as application of topical emollients and drugs, and giving encouragement to persist with therapy. The role of the family in promoting adherence to agreed treatment plans should not be underestimated. Therefore, understanding the experiences of family members, and identifying their needs may make a crucial contribution to the success of therapy.

Being able to measure the QoL impact of AD provides stark challenges to the health care team. Of course, the over-riding aim must be to effectively suppress the disease. Having identified the QoL problems we can no longer ignore them and we are obliged to creatively de-

velop methods to address these issues. We now have the tools to assess prospectively the impact of AD on QoL.

ACKNOWLEDGEMENT

Conflict of interest: FA has received honoraria and grants from Lilly, Janssen, Novartis, LEO, and Abbvie. JV has been on a paid advisory panel for Amgen. AYF is joint copyright owner of the DLQI, CDLQI, IDQoL, DFI, FDLQI and FROM-16. Cardiff University charges with-profit companies royalties when these quality of life questionnaires are used. AYF receives a share of these royalties according to Cardiff University policy.

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